REMARKS

Claims 7, 9, 11, 13, 15, 17, 19 and 20 are pending.

Claims 8,10, 12, 14, 16, and 18 are cancelled in order to put the case in order of allowance and without prejudice to the prosecution of their subject matter in other applications.

The claims are amended, and new claim 20, is added, to more particularly state and distinctly claim the subject matter which Applicants regard as their invention. Attached hereto are sheets showing the amendments to the claims, as well as a "clean set" of all pending claims, pursuant to 37 C.F.R. §1.121(c).

A substitute specification is provided, as required by the Examiner, to correct a number of typographical, grammatical, and spelling errors. A second substitute specification, marked to show the changes made to the original specification, is also provided, according to 37 C.F.R. §1.121(b)(3).

Neither the amendments to the claims, nor the new claim, nor the amendments contained in the substitute specification constitute new matter.

The claims are either objected to or rejected under 35 U.S.C. §103. For reasons to be set forth below, Applicants request that the rejections be removed and that the claims be allowed to issue.

1. The Objection To Claim 7 Is Obviated

Claims 7 and 8 are objected to as being duplicate claims. The Examiner states that the claims appear to be identical in scope and content because they differ only with respect to intended uses.

Applicants respectfully disagree, because claim 7 relates to methods of treating hepatitis whereas claim 8 relates to methods of treating neoplastic and immunologic disease, and therefore the claims do not cover the same subject matter; different uses for the same composition are distinct classes of subject matter, and are not duplicative.

Furthermore, because Applicants have cancelled claim 8, this rejection is rendered moot.

Accordingly, Applicants request that this rejection be withdrawn.

2. <u>The Claims Are Not Obvious Over The Cummins Citations</u>

Claims 7, 8, 11-14 and 17-19 are rejected under 35 U.S.C. §103 as obvious over either one of United States Patent No. 5,824,300 by Cummins ("the '300 patent") or International Patent Application Publication No. WO 88/03411 by Cummins ("the '411 application"), collectively, "the Cummins references".

According to the Examiner, the '300 patent and the '411 application describe aqueous formulations of human interferon which are suitable for use in the therapeutic methods it describes and claims. The Examiner states:

> Such methods call for delivery to the oropharyngeal mucosae of IFN in solution at dosages preferably ranging from about 0.5 to 1.5 IU per pound per day. . . For typical patients weighing from about 100 to 225 pounds (*ca.* 45-100 kg), the preferred dosages are thus on the order of 50 to 340 IU IFN-α per day. Among the preferred sources of IFN are buffy coat leukocytes. . . . Exemplary formulations described by Cummins contain 1-1500 IU of IFN in a dosage volume of one tablespoon (15ml), or 0.07-100 IUml^{-}.

The Examiner contends that it would have been obvious to prepare an aqueous solution in a convenient single dose delivery volume, such as one tablespoon. The Examiner further contends that "the intended uses recited in the instant claim impose no material or

functional limitations on the formulations *per se* or the methods of making them and thus do not patentably define over the prior art formulations."

The Applicants respectfully disagree. Claims 7, 9, 11, 13, 15, and 17 are all method of treatment claims, and as such, the intended use is critical to the claims. While the rejection might be applied to a composition claim having, as its only distinguishing limitation, an intended use, it is not applicable here, where the method of using the formulation- for treating viral hepatitis – is patentably distinct from the formulation itself. Furthermore, new claim 20 has limitations which make the intended use a critical feature of the claim (the composition must comprise a label providing instructions as to the manner of use).

The Cummins references make absolutely no teaching regarding the usefulness of oral α-interferon in treating viral hepatitis. Given the generally refractory nature of viral hepatitis to treatment, the effectiveness shown by the presently claimed invention should be considered unexpected. The effectiveness of the claimed methods in treating viral hepatitis is demonstrated by data presented in the instant specification at paragraphs 36-40 (page 7 line 10 through page 8 line12 of the originally filed specification), which showed that in fourteen patients suffering from hepatitis B infection, 50 percent of patients exhibited a stable remission of their disease after treatment with 150 Units of α-interferon per day, and also by data presented in the instant specification at paragraphs 41-44 (page 8 lines 13-32 of the originally filed specification), which shows that patients suffering from hepatitis C infection treated with 450 U of α-interferon per day demonstrated "a significant increase of vivacity and appetite, with a better tolerance to physical exercises" despite the fact that normalization of transaminase levels was not observed.

Furthermore, the Cummins references focus on the dosage of interferon administered but ignores the formulation, regarding solid, liquid, and gel formulations as being therapeutically equivalent. The present invention, however, is based, at least in part, on the discovery that *liquid* formulations show unexpectedly superior effectiveness.

As regards claim 19, Applicants assert that this claim is not obvious because neither of the Cummins references discloses an oral liquid formulation of α-interferon having a concentration of 100-500 IU/ml. Although Cummins does, in the context of a broad disclosure of various dosages and modes of administration, teach similar doses of interferon (albeit for different uses), the particular composition covered by claim 19 is not disclosed, Cummins favoring, as noted by the examiner, more dilute formulations of volumes more of the range of 1 tablespoon (15 ml).

Both in regard to the non-obviousness of the method claims as well as the composition claims, the use of liquid rather than solid forms of interferon is a critical aspect of the present invention. The importance of using liquid formulations is discussed in the present specification at paragraph 21, at page 4 lines 11-21 of the original specification, which indicates that the liquid formulation is readily accessible for absorption by the mucosa, whereas tablet forms must be dissolved:

> The preferred formulation in dosage units of small volumes (1 ml) to drink allows an immediate availability of the active principle, a good standard of cleanliness from the [*single dose*] primary container; the certainty of the taken dosage; the taking of the active principle to be immediately absorbed by the oro-pharyngeal mucosa, easily preventing the deglutition, an [*easy*] and safe way of adminsitration for all patients, [*as compared to*] lozenges or [*tablet*] formulations that should be kept in the mouth [*until completely dissolved*], with high chances [*that the formulation will be swallowed*].

The benefits of the liquid formulation are further supported by the Declaration Under Rule 132 submitted herewith ("the 132 Declaration). The 132 Declaration describes a

clinical study involving 30 patients having non-A, non-B or C hepatitis, who were treated with either (i) α-interferon in liquid form, at a concentration of 150 IU/ml, and a dose volume of 1 ml (total dose = 150 IU); (ii) α-interferon in tablet form, containing 150 IU/dose; or (iii) placebo. Ten patients were allocated to each patient group, and treatment continued for 24 weeks. Effectiveness of treatment was evaluated by monitoring serum alanine aminotransferase ("ALT") levels, performing liver biopsies before and after treatment, and by physically examining and questioning the patients.

As discussed on page 5 of the 132 Declaration, data regarding changes in ALT levels (depicted in Table 1 at page 8 of the 132 Declaration) indicated that patients treated with liquid α-interferon showed an overall response rate of 60%, as compared to rates of 30% in patients treated with α-interferon tablets and 10% in placebo-treated patients.

Hepatic biopsies showed significant histologic improvement in patients treated with α-interferon:

> The improvement is due primarily to a decrease in the [*severity of*] necrosis and degeneration in the labular and perportal regions that was observed in 80% (8/10) of the patients treated with interferon in the liquid form (vial) in 60% (6/10) of patients treated with interferon in the tablet form compared to the 20% (2/10) of patients treated with placebo. (page 6 of the 132 Declaration, referring to results depicted in Table 2.)

As further indicated in the Conclusion of the study, presented at page 7 of the 132 Declaration, the ALT levels for approximately half the α-interferon-treated responders remained normal for at least 6 months.

It is therefore clear from the specification, and supported by data contained in the 132 Declaration, that viral hepatitis may be effectively treated by liquid α-interferon at doses of 100-500IU per day, and that liquid formulations are substantially more effective than tablet

formulations. Neither discovery would have been expected in view of the Cummins references. Accordingly, it is respectfully requested that the rejection be removed.

3. The Claims Are Not Obvious Over Cummins And Ratajczak

Claims 9-10 and 15-16 are rejected under 35 U.S.C. §103 over either the '300 patent or the '411 application in view of Ratajczak et al., 1993, Arch. Immunol. Ther. Exp. 41:237-240 ("Ratajczak"). According to the Examiner, Ratajczak discloses the use of lozenges containing 50 or 100 IU of human lymphoblastoid interferon α for oropharyngeal delivery in the treatment of hepatitis B infections, and therefore supplies the deficiency whereby neither Cummins reference teaches lymphoblastoid cell-derived interferon. The Examiner contends:

> It would have been obvious to one having ordinary skill in the art at the time the invention was made to prepare an aqueous formulation of hIFN-α according to Cummins '300 or '411, employing lymphoblastoid IFN as described by Ratajczak in place of the buffy coat leukocyte INF noted particularly by Cummins, because Ratajczak evidences that lymphoblastoid IFN was readily available at the time of the invention and teaches that it is suitable for the treatment of an exemplary viral disease *via* delivery to the oropharyngeal mucosae.

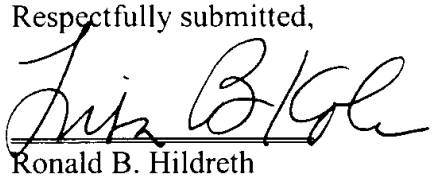
Applicants respectfully disagree, and assert that neither the '300 patent nor the '411 patent, alone or in any combination with Ratajczak, would render the claims obvious. As stated in response to the rejection over the Cummins references alone, a critical feature of the claimed invention is that it uses α-interferon in *liquid* form. This is in contrast to the teachings of Ratajczak, which employs lozenges and fails to appreciate the importance of administering IFN in liquid rather than solid form, as discussed in the specification and supported by the accompanying Rule 132 Declaration.

Therefore, the present rejection should be withdrawn.

4. Conclusion

For all the foregoing reasons, the rejections should be withdrawn and the claims should be allowed to issue. An early allowance is earnestly requested.

Respectfully submitted,



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REVISED CLAIMS SHOWING AMENDMENTS

7. (amended) A method of treating a subject having viral hepatitis [in a subject] comprising administering, to the subject, by the peroral route, an oral liquid formulation of natural human α-interferon at a daily dosage of between 100 and 500 IU.

11. (amended) The method of claim 7 wherein the human α-interferon is obtained from [a] lymphocyte cells.